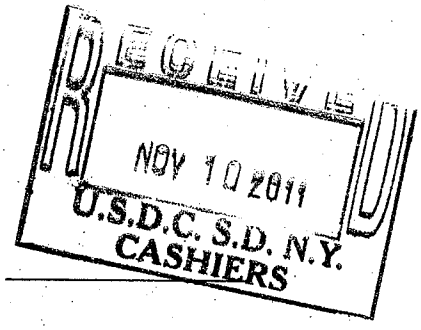
11 CIV 8130

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG,	:	Case No.
Plaintiffs,	:	
v.	:	
WATSON LABORATORIES, INC., WATSON PHARMA, INC., and WATSON PHARMACEUTICALS, INC.	:	
Defendants.	:	



COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd. and LTS Lohmann Therapie-Systeme AG (hereinafter "Plaintiffs"), for their Complaint herein against defendants Watson Laboratories, Inc., Watson Pharma, Inc., and Watson Pharmaceuticals, Inc. allege as follows:

NATURE OF ACTION

1. This is an action for patent infringement.

PARTIES

2. Plaintiff Novartis Pharmaceuticals Corporation ("NPC") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 59 Route 10, East Hanover, New Jersey 07936.

3. Plaintiff Novartis AG ("Novartis AG") is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

4. Plaintiff Novartis Pharma AG ("Pharma AG") is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

5. Plaintiff Novartis International Pharmaceutical Ltd. ("NIP") is a corporation organized and existing under the laws of Bermuda, having an office and place of business at Hurst Holme, 12 Trott Road, Hamilton HM LX, Bermuda.

6. Plaintiff LTS Lohmann Therapie-Systeme AG ("LTS") is a corporation organized and existing under the laws of Germany, having an office and place of business at Lohmannstraße 2, D-56626 Andernach, Germany.

7. On information and belief, Watson Laboratories, Inc. ("Watson Laboratories") is a corporation organized and existing under the laws of the State of Nevada, having a place of business at 311 Bonnie Circle, Corona, California, and another place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey.

8. On information and belief, Watson Pharma, Inc. ("Watson Pharma") is a corporation organized and existing under the laws of the State of Delaware, having a

place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey.

9. On information and belief, Watson Pharmaceuticals, Inc. ("Watson Pharmaceuticals") is a corporation organized and existing under the laws of the State of Nevada, having a place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey.

10. On information and belief, Watson Laboratories and Watson Pharma are wholly owned subsidiaries of Watson Pharmaceuticals.

11. On information and belief, the acts of Watson Laboratories complained of herein, were done at the direction of, with the authorization of, and with the cooperation, participation, and assistance of Watson Pharmaceuticals and Watson Pharma.

12. Defendants Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals are referred to collectively as "Watson."

JURISDICTION AND VENUE

13. This action arises under the patent laws of the United States of America. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331 and 1338(a).

14. On information and belief, Watson Pharmaceuticals organizes its operations by divisions—Generic, Brand, and Distribution—and reports its financial results in its Securities and Exchange Commission ("SEC") filings by reference to these divisions. Watson Pharmaceuticals consolidates its financial results with Watson subsidiaries in its SEC filings at least for 2007 to date and does not separate financial reports to the SEC for each Watson subsidiary.

15. On information and belief, the Generic Division is involved in the development, manufacture, marketing, sale, and distribution of generic pharmaceuticals. On information and belief, Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals each act as agents of each other and/or work in concert with each other to further the aims of the Generic Division. On information and belief, the Generic Division, which is responsible for, *inter alia*, developing and submitting abbreviated new drug applications ("ANDAs") to the U.S. Food and Drug Administration ("FDA"), relies on contributions from Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals.

16. On information and belief, the head of the Generic Division is an employee of Watson Pharmaceuticals, the Generic Division's ANDAs are submitted by Watson Laboratories, the Generic Division's products are manufactured also by Watson Laboratories, and the Generic Division's products are marketed and sold throughout the United States, including in New York and this Judicial District, by Watson Pharma.

17. On information and belief, Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals share a common place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey.

18. On information and belief, Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals each share with the others common employees, officers, and directors.

19. On information and belief, Watson Laboratories is registered as a domestic business corporation with the New York Department of State, Division of Corporations, with the DOS Process address: c/o CT Corporation System, 111 Eight

Avenue, New York, New York, 10011. On information and belief, Watson Laboratories is also registered as a Pharmacy Establishment in the State of New York by the New York Department of Education, Office of the Professions (Registration Nos. 026190 and 101186), which registrations are active. On information and belief, Watson Laboratories has purposely availed itself of the rights and benefits of New York law and this Court.

20. On information and belief, Watson Pharma is registered as a foreign business corporation with the New York Department of State, Division of Corporations, with the DOS Process address: c/o CT Corporation System, 111 Eight Avenue, New York, New York, 10011. On information and belief, Watson Pharma is also registered as a Pharmacy Establishment in the State of New York by the New York Department of Education, Office of the Professions (Registration Nos. 025849 and 026378), which registrations are active.

21. On information and belief, Watson Pharma is the distributor of drugs for which Watson Laboratories is the named applicant in the FDA's Approved Drug Product List. On information and belief, Watson Pharma, acting as the agent of Watson Laboratories and Watson Pharmaceuticals, markets and sells these drugs throughout the United States, including New York and this Judicial District.

22. On information and belief, Watson Laboratories and Watson Pharma are parties to one or more contractual agreements for distributing drugs manufactured under Watson Laboratories' ANDAs.

23. On information and belief, Watson Pharmaceuticals, through its own actions and the actions of one or more Watson subsidiaries, actively engages in a concerted effort to sell generic products throughout the United States, including in New

York and this Judicial District. On information and belief, Watson Pharmaceuticals owns properties and conducts business in this Judicial District in Carmel, New York, and at the following other locations in New York: Copiague, New York; and Grand Island, New York.

24. This Court has personal jurisdiction over defendants Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals under N.Y. C.P.L.R §§ 301, 302(a) and by virtue of, *inter alia*, the above-mentioned facts. They demonstrate that Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals either directly or through an agent, including each other, regularly do or solicit business in New York and this Judicial District, engage in other persistent courses of conduct in New York and this Judicial District, and/or derive substantial revenue from services or things used or consumed in New York and this Judicial District. These activities further demonstrate that Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals have continuous and systematic contacts in New York and this Judicial District.

25. On information and belief, Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals have acted or will act as agents of each other, and/or have worked or will work in concert with respect to the development, regulatory approval, marketing, sale and distribution of pharmaceutical products, including a rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosages.

26. On information and belief, each of Watson Laboratories, Watson Pharma, and Watson Pharmaceuticals, as part of Watson Pharmaceuticals's Generic Division, would manufacture, market, and/or sell within the United States Watson's rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosages, if FDA approval is granted.

27. On information and belief, if approved by the FDA, Watson's rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosages, would be marketed and distributed in New York and this Judicial District, prescribed by physicians practicing and dispensed by pharmacies located within New York and this Judicial District, and/or used by persons in New York and this Judicial District, all of which would have, and should be reasonably expected to have, consequences in New York and this Judicial District.

28. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b) and (c), and 28 U.S.C. § 1400(b).

CLAIM FOR RELIEF - PATENT INFRINGEMENT

29. Plaintiff NPC holds an approved new drug application ("NDA") No. 22-083 for Exelon® Patch (rivastigmine transdermal system or extended release film) (4.6 mg/24 hr and 9.5 mg/24 hr dosages), which patch contains the active ingredient rivastigmine. Exelon® Patch (4.6 mg/24 hr and 9.5 mg/24 hr) was approved by the United States Food and Drug Administration ("FDA") on July 6, 2007, and is indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease. Exelon® Patch (4.6 mg/24 hr and 9.5 mg/24 hr) is sold in the United States by Plaintiff NPC.

30. The active ingredient in the Exelon® Patch, rivastigmine, is known chemically as (S)- 3-[1-(dimethylamino) ethyl]phenyl ethylmethylcarbamate or (S)-[N-ethyl-3[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate].

31. Plaintiff Novartis AG is the owner of United States Letters Patent No. 5,602,176 ("the '176 patent"). The '176 patent was duly and legally issued on February 11, 1997.

32. Plaintiff Novartis AG was formed as a result of the merger of Ciba-Geigy AG and Sandoz Ltd., both of Basel, Switzerland. The '176 patent was initially assigned to Sandoz Ltd. on January 29, 1988, which subsequently became Novartis AG after the merger.

33. The '176 patent claims the (S)-[N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate] enantiomer substantially free of its (R) isomer in free base or acid addition form, as well as pharmaceutical compositions and methods of treating conditions such as Alzheimer's disease. A true copy of the '176 patent is attached hereto as Exhibit A.

34. Plaintiffs Novartis AG and LTS are the owners of United States Letters Patent No. 6,316,023 ("the '023 patent"). The '023 patent was duly and legally issued on November 13, 2001.

35. The '023 patent claims pharmaceutical compositions, *inter alia*, comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl-carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition, as well as transdermal devices. A true copy of the '023 patent is attached hereto as Exhibit B.

36. Plaintiffs Novartis AG and LTS are the owners of United States Letters Patent No. 6,335,031 ("the '031 patent"). The '031 patent was duly and legally issued on January 1, 2002.

37. The '031 patent claims pharmaceutical compositions, *inter alia*, comprising: (a) a therapeutically effective amount of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl-carbamate in free base or acid addition salt form; (b) about 0.01 to about 0.5 percent by weight of an antioxidant, based on the weight of the composition, and (c) a diluent or carrier, as well as transdermal devices. A true copy of the '031 patent is attached hereto as Exhibit C.

38. The '023 and '031 patents were initially assigned to Novartis AG and LTS Lohmann Therapie-Systeme GmbH Co. KG, which subsequently changed its legal form to become Plaintiff LTS.

39. On information and belief, Watson submitted to the FDA an ANDA under the provisions of 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of a rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosages ("Watson's ANDA Products"). On November 7, 2011, Kenton M. Walker, Esq., confirmed that the Watson entity that submitted the ANDA was defendant Watson Laboratories, a Nevada Corporation, having a place of business 311 Bonnie Circle, Corona, California. On information and belief, Mr. Walker is Senior Counsel, Intellectual Property, of defendant Watson Laboratories.

40. On information and belief, Watson submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of Watson's ANDA Products before the expiration of the '176, '023, and '031 patents.

41. By filing its ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of Watson's ANDA Products before the expiration of the '176, '023, and '031 patents, Watson has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, on information and belief, the commercial manufacture, use, offer for sale, sale and/or importation of Watson's ANDA Products, for which Watson seeks approval in its ANDA will also infringe one or more claims of the '176, '023, and '031 patents.

42. On information and belief, Watson's ANDA Products, if approved, will be administered to human patients in a therapeutically effective amount for treatment of mild to moderate dementia of the Alzheimer's type, which administration constitutes direct infringement of the '176 patent. On information and belief, this will occur at Watson's active behest, and with Watson's intent, knowledge and encouragement. On information and belief, Watson will actively induce, encourage and abet this administration with knowledge that it is in contravention of the rights under the '176 patent.

43. On information and belief, Watson made, and included in its ANDA, a certification under 21 U.S.C. § 355(j)(2)(vii)(IV) that, in its opinion and to the best of its knowledge, the '176, '023, and '031 patents are invalid, unenforceable and/or will not be infringed.

44. On information and belief, Watson's ANDA seeks approval to manufacture and sell Watson's ANDA Products, which infringe the '176, '023, and '031 patents.

45. Plaintiffs are entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of any approval of the aforementioned ANDA relating to Watson's ANDA Products, be a date that is not earlier than February 11, 2014, the expiration date of the '176 patent, and not earlier than January 8, 2019, the expiration date of the '023 and '031 patents, and an award of damages for any commercial sale or use of Watson's ANDA Products, and any act committed by Watson with respect to the subject matter claimed in the '176, '023, and '031 patents, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

46. On information and belief, when Watson filed its ANDA, it was aware of the '176, '023, and '031 patents and that the filing of its ANDA with the request for its approval prior to the expiration of the '176, '023, and '031 patents was an act of infringement of these patents.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

A. Judgment that Watson has infringed one or more claims of the '176, '023, and '031 patents by filing the aforesaid ANDA relating to Watson's rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosages;

B. A permanent injunction restraining and enjoining Watson and its officers, agents, attorneys and employees, and those acting in privity or concert with it, from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of a rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosages, as claimed in the '176, '023, and '031 patents;

C. An order that the effective date of any approval of the aforementioned ANDA relating to Watson's rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosages, be a date that is not earlier than the expiration of the right of exclusivity under the '176, '023, and '031 patents;

D. Damages from Watson for the infringement of the '176, '023, and '031 patents;

E. The costs and reasonable attorney fees of Plaintiffs in this action; and

F. Such other and further relief as the Court may deem just and proper.

Dated: November 10, 2011

FITZPATRICK, CELLA, HARPER & SCINTO

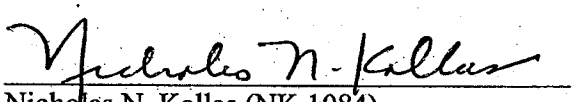


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EXHIBIT A

US005602176A

United States Patent [19]

Enz

[11] Patent Number: 5,602,176

[45] Date of Patent: Feb. 11, 1997

[54] **PHENYL CARBAMATE**

[75] Inventor: **Albert Enz**, Basel, Switzerland

[73] Assignee: **Sandoz Ltd.**, Basel, Switzerland

[21] Appl. No.: **466,502**

[22] Filed: **Jun. 6, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 353,848, Dec. 24, 1994, abandoned, which is a continuation of Ser. No. 110,622, Aug. 23, 1993, abandoned, which is a continuation of Ser. No. 6,904, Jan. 21, 1993, abandoned, which is a continuation of Ser. No. 925,365, Aug. 4, 1992, abandoned, which is a continuation of Ser. No. 859,171, Mar. 27, 1992, abandoned, which is a continuation of Ser. No. 750,334, Aug. 27, 1991, abandoned, which is a continuation of Ser. No. 664,189, Mar. 4, 1991, abandoned, which is a continuation of Ser. No. 589,343, Sep. 27, 1990, abandoned, which is a continuation of Ser. No. 408,640, Sep. 18, 1989, abandoned, which is a continuation of Ser. No. 285,177, Dec. 15, 1988, abandoned, which is a continuation of Ser. No. 162,568, Mar. 1, 1988, abandoned.

[30] **Foreign Application Priority Data**

Mar. 4, 1987 [DE] Germany 37 06 914.4

[51] **Int. Cl.**^{6} **A61K 31/27**

[52] **U.S. Cl.** **514/490**; 560/136

[58] **Field of Search** 560/136; 514/490

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,469,700 9/1984 Somers 424/265

FOREIGN PATENT DOCUMENTS

193926 9/1986 European Pat. Off. .

Primary Examiner—Michael L. Shippen

Attorney, Agent, or Firm—Robert S. Honor; Melvyn M. Kassenoff; Thomas O. McGovern

[57] **ABSTRACT**

The (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylncarbamate in free base or acid addition salt form is useful as pharmaceutical, particularly for systemic transdermal administration.

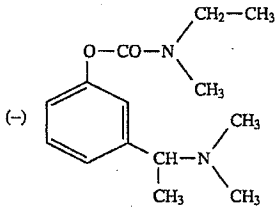
12 Claims, No Drawings

PHENYL CARBAMATE

This is a continuation of application Ser. No. 08/353,848 filed Dec.12, 1994, which in turn is a continuation of application Ser. No. 08/110,622, filed Aug. 23, 1993, which in turn is a continuation of application Ser. No. 08/006,904, filed Jan. 21, 1993, which in turn is a continuation of application Ser. No. 07/925,365, filed Aug. 4, 1992, which in turn is a continuation of application Ser. No. 07/859,171, filed Mar. 27,1992, which in turn is a continuation of application Ser. No. 07/750,334, filed Aug. 27,1991, which in turn is a continuation of application Ser. No. 07/664,189, filed Mar. 4, 1991 which in turn is a continuation of application Ser. No. 07/589,343, filed Sep. 27, 1990, which in turn is a continuation of application Ser. No. 07/408,640, filed Sep. 18, 1989, which in turn is a continuation of application Ser. No. 07/285,177, filed Dec. 15, 1988, which in turn is a continuation of application Ser. No. 07/162,568, filed Mar. 1, 1988, all now abandoned.

The present invention relates to a novel phenyl carbamate with anticholinesterase activity.

More particularly the invention relates to the (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate of formula I



I

in free base or acid addition salt form.

As can be seen from this formula, in free base form the sign of rotation of the compound of formula I is (–). However in acid addition salt form it may be (+) or (–). For instance the sign of rotation of the hydrogen tartrate is (+). The present invention covers the free base form as well as the acid addition salt forms, independently of their sign of rotation.

The racemic mixture (±)-N-ethyl-3-[(1-dimethylamino-)ethyl]-N-methyl-phenyl-carbamate in form of its hydrochloride is known from the European patent application 193,926 where it is identified as RA_7 HCl.

According to this disclosure the racemate in free base form is obtained by amidation of α-m-hydroxyphenylethyldimethylamine with a corresponding carbamoyl halogenide. The resulting compound and its pharmacologically acceptable acid addition salts, which can be prepared from the free base in known manner, are disclosed as acetylcholinesterase inhibitors in the central nervous system.

It has now surprisingly been found that the (–)-enantiomer of formula I and its pharmacologically acceptable acid addition salts, hereinafter referred to as compounds according to the invention, exhibit a particularly marked and selective inhibition of the acetylcholinesterase.

These findings are unexpected, particularly since it is not believed that the dialkylaminoalkyl side chain, which contains the optically active centre, is mainly responsible for the acetylcholinesterase inhibiting activity of the phenyl carbamates.

The compounds according to the invention have never been specifically disclosed in the literature. The free base may be prepared from the racemate by separation of the enantiomers in accordance with known methods, e.g. using di-0,0'-p-toluyl-taratric acid. The acid addition salts may be prepared from the free base in known manner. These include e.g. the hydrogen tartrate.

The compounds according to the invention exhibit pharmacological activity as indicated in standard tests and are therefore useful as pharmaceuticals. They reach the central nervous system rapidly after s.c., i.p. or p.o. administration in rats. They exert a brain region-selective inhibition of acetylcholinesterase activity, hippocampal and cortical enzyme being more inhibited than acetylcholinesterase originating from striatum and pons/medulla. Furthermore they have a long duration of action.

The following results, for example, illustrate the pharmacological profile of the compounds according to the invention as compared to the corresponding isomers and racemates. Compound A is the compound of formula I in form of its hydrogen tartrate. Compound B is the optical isomer of said salt. C designates the racemic mixture of the compound of formula I and its optical isomer, in form of the hydrochloride.

In Vitro Assays

Electrically evoked ^{3}H-acetylcholine release from rat hippocampal slices

Electrically evoked ^{3}H-acetylcholine (^{3}H-ACh) release from rat hippocampal slices is a functional in vitro model to investigate presynaptic muscarinic autoreceptor agonists and antagonists. This model can also be used as an indirect method to evaluate drugs which inhibit acetylcholinesterase (AChE). Inhibition of AChE activity leads to the accumulation of endogenous ACh which then interacts with presynaptic muscarinic autoreceptors and inhibits further release of ^{3}H-ACh.

Rat hippocampal slices (Wistar strain, 180–200 g) are prepared by chopping into cross sections whole hippocampal slices at a distance of 0.3 mm with a McIlwain tissue chopper. Hippocampal slices obtained from 3 rats are incubated for 30 min. at 23° C. in 6 ml Krebs-Ringer containing 0.1 uCi ^{3}H-choline and transferred into the superfusion chamber and superfused with Kreb's medium containing 10 μM hemicholinium-3 at a rate of 1.2 ml/min. at 30° C. Collection of 5 min. fractions of the superfusate begins after 60 min. of superfusion. Two periods of electrical stimulation (2 Hz rectangular pulses 2 msec, 10 mA, 2 min.) are applied after 70 min. (S_1) and after 125 min. (S_2) of superfusion. Test substances are added 30 min. before S_2 and are present in the superfusion medium until 145 min. of superfusion. At the end of the experiments the slices are solubilized in conc. formic acid and tritium content is determined in the superfusate and the solubilized slices. Tritium outflow is expressed as the fractional rate of tritium outflow per min. Electrically evoked tritium outflow is calculated by subtraction of the extrapolated basal tritium outflow from the total tritium outflow during the two min. of electrical stimulation and the following 13 min. and is expressed as percent of the tritium content at the beginning of the sample collection. Drug effects on stimulation evoked tritium outflow are expressed as the ratios S_2/S_1. All experiments are run in dublicates using a programmable 12 channel superfusion system. For the calculation a computer program is used.

In this test compound A inhibits electrically evoked ^{3}H-ACh release from hippocampal slices by approximately 40% (100 μM) while racemate C (100 μM) inhibits by approximately 25%. The inhibitory effects of compound A and racemate C can be antagonized by atropine. These results are compatible with an AChE-inhibiting activity. Compound B is inactive in this model.

Acetylcholinesterase inhibition in different rat brain regions

AChE preparations of different rat brain regions (Cortex, hippocampus and striatum) are used in this test and the IC_{50} (inhibitory concentrations in μM) are determined. The enzyme preparations are preincubated with the inhibitor 15 minutes before the determination.

The AChE activity is measured according to the method described by Ellman (Arch. Biochem. Biophys. 82, 70, 1959). Rat brain tissue is homogenized in cold phosphate buffer pH 7.3 (0.25 mM) containing 0.1% of Triton X-100. After centrifugation aliquots of the clear supernatant is used as enzyme source. The enzyme is preincubated with different concentrations of the inhibitor. After different times, substrate (acetylthiocholinjodide 0.5 mM) is added and the remaining activity determined.

The results are given in the following table 1:

TABLE 1

IC_{50}	Cortex	Hippocampus	Striatum
Compound A	2.8	3.7	3.0
Compound B	16.1	14.5	13.8
Racemate C	3.2	3.9	3.2

As can be seen from this table the AChE inhibition with compound A is slightly superior than that with racemate C, whereas compound B is significantly less active.

Acetylcholinesterase inhibition ex vivo in different rat brain regions

30 minutes after administration of different doses of compound A, the AChE activity in different rat brain regions is measured ex vivo. The method is as disclosed above. The IC_{50} values found are 7 μmol/kg p.o. in striatum, 4 μmol/kg p.o. in hippocampus and 2 μmol/kg p.o. in cortex. The IC_{50} obtained after administration of the racemate C are for all examined regions about 2–3 times higher. Six hours after administration of compound A (10 μmol/kg p.o.) the AChE in striatum is still inhibited by 16%, whereas at the same time the activities in cortex and hippocampus are inhibited by 39% and 44% respectively.

In Vivo Assays

Influence on dopamine metabolism

Male OFA rats (150–200 g) were used both for acute and subchronic experiments. The animals are maintained under 12 hour periods of light and dark. The animals are sacrificed always between 11.00 and 13.00 h. The brains are excised immediately, dissected on ice according to the method of GLOWINSKI and IVERSEN, J. Neurochem. 13, 655 (1966), frozen on dry ice and the tissue samples stored at −80° C. until analysis.

Dopamine and its metabolites DOPAC (3,4-dihydroxyphenylacetic acid) and HVA (homovanillic acid) are determined in brain tissue extracts which are obtained by homogenisation of the stored brain tissue samples in 0.1N HCl containing 0.05 mM ascorbic acid and subsequent centrifugation. Striatal and cortical tissues are used.

The determination of the metabolites is performed using either the gas chromatography/mass fragmentography (GCMS) technique as described by KAROUM et al., J. Neurochem. 25, 653 (1975) and CATABENI et al., Science 178, 166 (1972) or the fluorometric method as described by WALDMEIER and MAITRE, Analyt. Biochem. 51, 474 (1973). For the GCMS method, tissue extracts are prepared by adding known amounts of deuterated monoamines and their respective metabolites as internal standards.

Dopamine metabolism in striatum is increased following the administration of compounds A and B and racemate C (This property is a consequence of the acetylcholine accumulation provoked by said compounds). However compound A is more active than compound B and racemate C in enhancing the striatal dopamine metabolite concentration.

Muscarinic and nicotinic effects on brain glucose utilisation

Changes in the functional activity of the CNS are associated with altered deoxyglucose (DOG) utilisation in the brain which can be visualised simultaneously in several brain regions using the autoradiographic method of Sokoloff et al., J. Neurochem. 28, 897 (1977). The administration of cholinergic drugs either direct (muscarinic agonists) or indirect (accumulation of acetylcholine) induces in this model a characteristic "fingerprint" pattern by modifying the regional glucose metabolism.

Male Wistar rats (150–200 g) are used. Drugs are administered at various doses and by different routes (i.v., p.o., i.p.) to animals. [14C]-2-deoxyglucose (125 μC/kg) is injected 45 min. before the animals are sacrificed. The brains are immediately excised, frozen at −80° C. and subsequently cut in slices with a thickness of 20 μm. The optical densities of the radiographic images are measured according to a modification of Sokoloff et al.

After p.o. application of compounds A and B (7.5 μmol/kg) significant changes in DOG utilisation in various rat brain regions are observed. The effect of compound A is more potent than that of compound B during the initial 30 minutes. The most marked changes are found in the visual regions and the anteroventral thalamus and also in the lateral habenula mucleus.

Acetylcholine levels in different rat brain regions

The effects of compounds A and B and racemate C as AChE inhibitors in vivo is determined by measuring the levels of ACh in different regions of rat brain at various times after drug administration.

OFA rats (200–230 g) are used. The animals are killed by microwave irradiation focused on the head (6 kW operating power 2450 Mhz exposure 1.7 sec., Pueschner Mikrowellen-Energietechnik, Bremen). The brains are removed dissected according to Glowinski and Iversen (1966) and stored at −70° C. until analysis. The brain parts are homogenized in 0.1M perchloric acid containing internal deuterated standards of ACh-d_4 and Ch(choline)-d_4. After centrifugation, endogenous ACh and Ch together with their deuterated variants are extracted with dipicrylamine (2,2',4,4',6,6'-hexanitrodiphenylamine) in dichlormethane as ion pairs. The Ch moities are derivatized with propionyl chloride and the resulting mixture of ACh and propyl choline derivatives are demethylated with sodiumbenzenethiolate and analyzed by mass-fragmentography according to Jenden et al. Anal. Biochem., 55, 438–448, (1973).

A single application of 25 μmol/kg p.o. increases ACh concentrations in striatum, cortex and hippocampus. The maximal effect is achieved about 30 min. after oral application and declines during the next 3–4 hours. In cortex and hippocampus the ACh levels are still significantly higher at 4 hours compared to controls. The effects are dose dependent. The influence of compound B is significantly weaker than that induced by racemate C, and the influence of racemate C is significantly weaker than that induced by compound A.

Furthermore the compounds according to the invention are indicated to be well tolerated and orally active, and they have a long duration of action, e.g. in the above and other standard tests.

The compounds according to the invention are therefore useful for the treatment of senile dementia, Alzheimer's

disease, Huntington's chorea, tardive dyskinesias, hyperkinesia, mania, acute confusion disorders, Down's syndrome and Friedrich's ataxia.

For these indications, the appropriate dosage will, of course, vary depending upon, for example, the compound according to the invention employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at daily dosages from about 0.01 to about 10 mg/kg, e.g. about 0.1 to about 5 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 0.1 to about 25 mg, e.g. about 0.1 to about 5 mg of a compound according to the invention, conveniently administered, for example, in divided doses up to four times a day.

The compounds according to the invention may be administered by any conventional route, in particular enterally, preferably orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions.

The above mentioned compound A is the preferred compound for the above mentioned indications. The preferred indication is senile dementia.

The present invention also provides pharmaceutical compositions comprising a compound according to the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.025 to about 12.5 mg of a compound according to the invention. Conveniently an acid addition salt form is used. The preferred salt form is compound A, especially for orally administrable forms, e.g. from the point of view of stability.

In the following example, the temperatures are uncorrected and are in degrees centigrade.

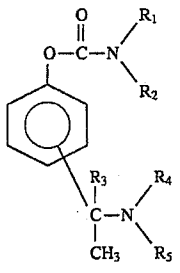
EXAMPLE 1

(S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate

130 g of (±)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylcarbamate and 210 g of (+)-di-0,0'-p-toluoyl tartaric acid monohydrate are dissolved while heating in 1.3 liter of methanol/water (2:1). The salt precipitated after cooling is filtered and recrystallised 3 times from methanol/water (2:1). The (S)-enantiomer is released by partitioning between 1N NaOH and ether. $[\alpha]D_D^{20}=-32.1°$ (c=5 in ethanol).

The hydrogen tartrate of the title compound (from ethanol) melts at 123°–125°. $[\alpha]_D^{20}=+4.7°$ (c=5 in ethanol).

The present invention furthermore provides the systemic transdermal application of the phenyl carbamates of formula I',



I'

wherein

R_1 is hydrogen, lower alkyl, cyclohexyl, allyl or benzyl,

R_2 is hydrogen, methyl, ethyl or propyl, or

R_1 and R_2 together with the nitrogen to which they are attached form a morpholino or piperidino radical,

R_3 is hydrogen or lower alkyl,

R_4 and R_5 are the same or different and each is a lower alkyl, and the dialkylaminoalkyl group is in the meta, ortho or para position,

in free base or pharmaceutically acceptable acid addition salt form.

The compounds of formula I' and their pharmaceutically acceptable acid addition salts as well as their preparation and their use as acetylcholinesterase inhibitors are known from the above mentioned European patent application 193,926.

The compounds of formula I' include for example the above defined compound A and racemate C.

It has now surprisingly been found that the compounds of formula I' in free base or pharmaceutically acceptable acid addition salt form, hereinafter referred to as compounds for administration according to the invention, exhibit unexpectedly good skin penetration when administered percutaneously.

The penetration through the skin of the compounds for administration according to the invention may be observed in standard in vitro or in vivo tests.

One in vitro test is the well known diffusion test which may be effected according to the principles set out in GB 2098865 A and by T. J. Franz in J. Invest. Dermatol. (1975) 64, 194–195. Solutions containing the active agent in unlabelled or radioactively labelled form are applied to one side of isolated pieces of intact human skin or hairless rat skin about 2 cm^2 in area. The other side of the skin is in contact with physiological saline. The amount of active agent in the saline is measured in conventional manner, e.g. by HPLC or spectrophotometric techniques, or by determining the radioactivity.

In this test using rat skin the following penetration rates, for example, have been found:

Above defined compound A: 23.6±14.9%

Compound of formula I in free base form: 28.0±8.2%

Moreover it has been found that transdermal administration of the compounds for administration according to the invention induces a long-lasting and constant inhibition of acetylcholinesterase activity as indicated in standard tests, with a slow onset of action, which is particularly advantageous with respect to the tolerability of these compounds.

For example the acetylcholinesterase inhibition in different rat brain regions ex vivo has been measured after transdermal administration of the compounds for administration according to the invention, and compared to the inhibition obtained after administration via different routes.

The compounds are dissolved in or diluted with n-heptane to a concentration of 1 or 3 mg/20 µl. Male rats (OFA strain, ca. 250 g) are shaved in the neck region and the solution is applied with a micropipette on the skin. The application place is immediately covered using a thin plastic film and a plaster. The animal has no access to the plaster. Various times after the administration the animals are killed by decapitation and the remaining AChE activity is measured.

Transdermal administration of the above defined compound A, for example, induces a long-lasting, dose-dependent inhibition of AChE activity. In contrast to the rapid onset of the effect after either oral or subcutaneous application (max. 15 and 30 min. respectively), the AChE inhibition occurs slowly after this application route (max.>2

hours) without affecting the brain region selective AChE inhibition.

The results are shown in the following table 2. Twenty four hours after transdermal application, the AChE activity is still inhibited in central and peripheral regions. After the same time, orally applied compound A has no effect on the enzyme, whereas after the s.c. application only the enzyme in the heart is significantly inhibited.

TABLE 2

Time after Treatment	n	AChE activity in % of controls ± SD Cortex	Hippocampus	Striatum	Pons/Medulla	Heart	Blood
Transdermal 30 µmol/kg							
0.5 hours	6	86.1 ± 5.6	86.7 ± 5.9	89.7 ± 8.4	91.5 ± 3.8	109.0 ± 9.3	71.3 ± 12.3
6 hours	6	42.4 ± 11.7	45.7 ± 15.0	65.9 ± 15.5	53.6 ± 13.3	52.0 ± 13.1	41.9 ± 13.1
24 hours	6	73.8 ± 5.7	80.4 ± 8.8	81.0 ± 8.2	85.3 ± 4.2	63.9 ± 12.5	78.1 ± 17.8
Oral 10 µmol/kg							
0.5 hours	6	21.0 ± 3.5	19.7 ± 3.8	32.9 ± 10.7	26.6 ± 4.0	71.2 ± 11.2	34.0 ± 2.0
6 hours	6	65.3 ± 21.3	62.0 ± 15.4	87.5 ± 8.8	80.3 ± 9.2	101.0 ± 7.0	77.2 ± 14.7
24 hours	6	99.2 ± 8.9	97.2 ± 7.1	96.7 ± 3.3	104.1 ± 6.8	94.2 ± 9.2	97.2 ± 13.8
Subcutaneous 8 µmol/kg							
0.5 hours	6	16.8 ± 2.0	18.3 ± 3.1	28.2 ± 12.2	20.9 ± 2.9	33.3 ± 5.6	17.4 ± 4.1
6 hours	6	85.1 ± 1.6	81.4 ± 7.6	82.9 ± 2.8	87.1 ± 4.1	51.0 ± 17.9	79.5 ± 8.2
24 hours	6	93.8 ± 5.9	99.9 ± 9.9	91.0 ± 2.3	98.7 ± 6.0	65.7 ± 21.2	105.7 ± 16.8

Control values (pmole/mg × min. ± SD n = 15):
Cortex: 3.67 ± 0.30
Hippocampus: 4.42 ± 0.30
Striatum: 33.8 ± 3.08
Pons/Medulla: 7.98 ± 0.36
Heart: 2.27 ± 0.39
Blood: 311.4 ± 44.2

Thus in another aspect the present invention provides a pharmaceutical composition for systemic transdermal administration incorporating as an active agent a compound of formula I' in free base or pharmaceutically acceptable acid addition salt form.

In a further aspect the present invention provides a method of systemically administering an active agent of formula I' in free base or pharmaceutically acceptable acid addition salt form which comprises administering the active agent to the skin.

The active agents may be administered in any conventional liquid or solid transdermal pharmaceutical composition, e.g. as described in Remington's Pharmaceutical Sciences 16th Edition Mack; Sucker, Fuchs and Spieser, Pharmazeutische Technologie 1st Edition, Springer and in GB 2098865 A or DOS 3212053 the contents of which are incorporated herein by reference.

Conveniently the composition is in the form of a viscous liquid, ointment or solid reservoir or matrix. For example the active agent is dispersed throughout a solid reservoir or matrix made of a gel or a solid polymer, e.g. a hydrophilic polymer as described in European Patent Application No. 155,229.

The active agent may be incorporated in a plaster.

The compositions for transdermal administration may contain from about 1 to about 20% by weight of active agent of formula I' in free base or pharmaceutically acceptable acid addition salt form.

The pharmaceutical compositions for transdermal administration may be used for the same indications as for oral or intravenous administration. The amount of pharmaceutically active agent to be administered will individually depend on the drug release characteristics of the pharmaceutical compositions, the drug penetration rate observed in in vitro and in vivo tests, the potency of active agent, the size of the skin contact area, the part of the body to which the unit is stuck, and the duration of action required. The amount of active agent and area of the pharmaceutical composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of the active agent in a pharmaceutical composition according to the invention to intact skin and blood levels of active agent observed after oral or intravenous administration of a therapeutically effective dose of the pharmacologically active agent.

Given the daily dose of a drug for oral administration, the choice of a suitable quantity of drug to be incorporated in a transdermal composition according to the invention will depend upon the pharmacokinetic properties of the active agent, including the first pass effect; the amount of drug which can be absorbed through the skin from the matrix in question for a given area of application and in a given time; and the time for which the composition is to be applied. Thus, a drug with a high first pass effect may require a relatively low quantity in the transdermal composition when compared with the oral daily dose, since the first pass effect will be avoided. On the other hand, generally a maximum of only approximately 50% of the drug in the matrix is released through the skin in a 3 day period.

The pharmaceutical compositions of the invention in general have for example an effective contact area of drug reservoir on the skin of from about 1 to about 50 square centimeters, preferably about 2 to 20 square centimeters, and are intended to be applied for from 1–7 days, preferably 1–3 days.

Compound A may for example be administered at a dose of 10 mg in a patch of ca. 10 cm^2, once every three days.

The following example illustrates the invention.

EXAMPLE 2

Preparation of a Transdermal Composition Containing a Hydrophilic Polymer

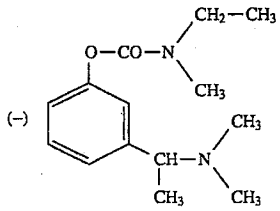
Composition	
Compound of formula I', e.g. compound A	20%
Hydrophilic polymer, e.g. Eudragit E 100*	30%
Non swellable acrylate polymer, e.g. Durotack 280–2416**	44%
Plasticizer, e.g. Brij 97***	6%

*Registered Trade Mark, available from Röhm, Darmstadt, W. Germany
**Registered Trade Mark, available from Delft National Chemie Zutphen, Netherlands
***Registered Trade Mark, available from Atlas Chemie, W. Germany

The components are added to acetone or ethanol or another appropriate volatile organic solvent and mixed to give a viscous mass. The mass is spread on top of an aluminised polyester foil (thickness 23 microns) using a conventional apparatus, to produce a film of thickness 0.2 mm when wet. The film is allowed to dry at room temperature over 4 to 6 hours. The aluminium foil is then cut up into patches about 10 sq cm in area.

What we claim is:

1. The (S)-[N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate] enantiomer of formula I substantially free of its (R) isomer



I

in free base or acid addition form.

2. The compound of claim 1 which is the hydrogen tartrate salt of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenylcarbamate.

3. A pharmaceutical composition which comprises a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

4. A method of treating senile dementia, which comprises administering a therapeutically effective amount of a compound of claim 1 in free base or pharmacologically acceptable acid addition salt form to a subject in need of such treatment.

5. A method of treating Alzheimer's disease, which comprises administering a therapeutically effective amount of a compound of claim 1 in free base or pharmacologically acceptable acid addition salt form to a subject in need of such treatment.

6. A method of treating Huntington's chorea, tardive dyskinesias, hyperkinesia, mania, acute confusion disorders, Down's syndrome or Friedrich's ataxia, which comprises administering a therapeutically effective amount of a compound of claim 1 in free base or pharmacologically acceptable acid addition salt form to a subject in need of such treatment.

7. A method of systemically administering a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, which comprises administering the active agent transdermally through the skin.

8. A systemic transdermal pharmaceutical composition according to claim 3 comprising a therapeutically effective amount of (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenyl-carbamate in free base or pharmaceutically acceptable acid addition salt form, and a pharmaceutically acceptable carrier therefor suitable for systemic transdermal administration.

9. A systemic transdermal pharmaceutical composition according to claim 3 comprising a therapeutically effective amount of the hydrogen tartrate salt of (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenyl-carbamate, and a pharmaceutically acceptable carrier therefor suitable for systemic transdermal administration.

10. A systemic transdermal pharmaceutical composition according to claim 8 in which the (S)-N-ethyl-3-[(1-dimethyl-amino)ethyl]-N-methyl-phenyl-carbamate is in free base form.

11. A systemic transdermal pharmaceutical composition according to claim 8 in which the pharmaceutically acceptable carrier is a transdermal patch.

12. A method according to claim 7 in which the compound is in free base form.

* * * * *

EXHIBIT B

US006316023B1

(12) **United States Patent**
Asmussen et al.

(10) **Patent No.: US 6,316,023 B1**
(45) **Date of Patent: *Nov. 13, 2001**

(54) **TTS CONTAINING AN ANTIOXIDANT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/747,519**

(22) Filed: **Dec. 20, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/291,498, filed on Apr. 14, 1999, which is a continuation-in-part of application No. PCT/EP99/00078, filed on Jan. 8, 1999.

(30) **Foreign Application Priority Data**

Jan. 12, 1998 (GB) 9800526

(51) **Int. Cl.**[7] **A61K 9/70**

(52) **U.S. Cl.** **424/449**; 424/448; 602/57; 602/60; 604/290; 604/305; 604/307

(58) **Field of Search** 424/449, 448; 602/57, 60; 604/290, 305, 307

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,948,807	*	8/1990	Rosin et al.	514/484
5,344,656	*	9/1994	Enscore et al.	424/448
5,462,745	*	10/1995	Enscore et al.	424/448
5,602,176	*	2/1997	Enz	514/490

FOREIGN PATENT DOCUMENTS

0 427 741 B1	*	5/1991	(EP) .
2 611 707	*	9/1988	(FR) .
89/12470	*	12/1989	(WO) .
98/30243	*	7/1998	(WO) .
98/31356	*	7/1998	(WO) .

OTHER PUBLICATIONS

Schneider, J Clin Psychiatry, (suppl 14), "New Therapeutic Approaches to Alzheimer's Disease", vol. 57, pp 30–36 (1996).

Sano, et al, The New England Journal of Medicine, "A Controlled Trial of Selegiline, Alpha–Tocopherol, or Both as Treatment for Alzheimer's Disease", vol. 336, No. 17, pp. 1216–1222 (1997).

Schneider et al., Am J Psychiatry, "A Double–Blind Crossover Pilot Study of I–Deprenyl (Selegiline) Combined With Cholinesterase Inhibitor in Alzheimer;'s Disease", vol. 150, No. 2, pp. 321–323 (1993).

Sunderland, et al., International Psychogeriatrics, "A Strategy of "Combination Chemotherapy" in Alzheimer's Disease: Rationale and Preliminary Results with Psysostigmine plus Deprenyl". Vol. 4 Suppl. 2, pp. 291–309 (1992).

* cited by examiner

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(57) **ABSTRACT**

Pharmaceutical composition comprising (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in free base or acid addition salt form and an antioxidant. Said pharmaceutical compositions may be delivered to a patient using a transdermal delivery device.

9 Claims, No Drawings

TTS CONTAINING AN ANTIOXIDANT

This application is a continuation of U.S. application Ser. No. 09/291,498, filed Apr. 14, 1999, which is a continuation-in-part of International Application No. PCT/EP99/00078, filed Jan. 8, 1999.

This invention relates to a pharmaceutical composition for systemic administration of a phenyl carbamate, e.g. by transdermal administration. In particular this invention relates to a pharmaceutical composition of the phenyl carbamate—(S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate—(hereinafter referred to as compound A) in free base or acid addition salt form as disclosed in published UK patent application GB 2 203 040, the contents of which are incorporated herein by reference.

Compound A is useful in inhibiting acetylcholinesterase in the central nervous system, e.g. for the treatment of Alzheimer's disease.

A transdermal composition in the form of a patch is described in Example 2 of GB 2,203,040 according to which compound A is mixed with two polymers and a plasticiser to form a viscous mass. This mass is applied to a foil which is cut into patches.

It has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen. The transdermal composition described in GB 2203040 has been found to degrade, possibly by oxidative degradation, despite the formation of an occlusive polymer matrix around compound A and its storage in air-tight packaging.

The present applicant has found that stable pharmaceutical compositions comprising compound A can now be obtained, which show insignificant degradation of compound A over a prolonged time period, e.g. 2 years, as indicated by standard tests, e.g. stress tests.

In one aspect, the invention provides a pharmaceutical composition comprising Compound A in free base or acid addition salt form and an anti-oxidant.

The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests.

The pharmaceutical compositions of the invention may contain high amounts of compound A, e.g. from 1 to 40% by weight, e.g. 10–35%, more particularly 20–35%, e.g. 30%.

The compound A may be in any of a wide variety of pharmaceutical diluents and carriers known in the art. The diluent or carrier may contain trace amounts of free radicals without affecting the stability of the pharmaceutical composition of the invention.

The diluent or carrier is preferably one or more polymers, more preferably a hydrophilic polymer or polymers. In a preferred embodiment the diluent of carrier is selected from at least one polymer selected from acrylate polymers, and polymethacrylate polymers. The polymers preferably have a mean molecular weight of from about 50,000 to about 300,000 Daltons, e.g. 100,000 to 200,000 Daltons. The polymers preferably are capable of forming a film, thus to be compatible to the skin.

As a polymer one can mention in particular an acrylate co-polymer, e.g. co-polymers of butyl acrylate, ethyl hexyl acrylate and vinyl acetate. Preferably the polymer is cross-linked. A preferred acrylate polymer is one of the Durotak brand available from National Starch and Chemical Company, Zutphen, Holland, e.g. Durotak 87-2353 (hereinafter polymer A), 387-2051 or 387-2052 (hereinafter polymer D).

The diluent or carrier is preferably present in an amount of up to 90%, more preferably 70% by weight base on the total weight of the pharmaceutical composition.

The polymer, when a hydrophilic polymer, may conveniently take up water and is permeable to water, e.g. moisture from the skin, although the polymer may be insoluble in water. The polymer may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum corneum at a pH of from 4 to 7, preferably at skin pH, e.g. around 5.5. If desired such polymers may be soluble in organic solvents.

Examples of suitable polymers include polyacrylamide and its co-polymers, polyvinylpyrrolidone (PVP), vinyl acetate/vinyl alcohol co-polymers, polyvinyl alcohol (PVA) and derivatives, ethyl cellulose and other cellulose and starch derivatives.

Hydrophilic polyacrylates are preferred polymers. The polyacrylate may be substituted, e.g. a methacrylate. They may be commercially available acrylate/methacrylate co-polymers. Some or all of the acid groups may be esterified, e.g. with alkyl (C_{1-10}) groups, more particularly alkyl groups having 1 to 4 carbon atoms such as methyl or ethyl groups.

Examples of commercially available polymers of this type include:

1) Polymers of methacrylate containing alkyl (C_{1-4}) ester groups. Preferably the polymer matrix is a mixture of an acrylate polymer and a methacrylate polymer e.g. in a weight ratio of from 5:1 to 1:1, e.g. 4:1 to 2:1 e.g. 3:1, e.g. butylmethylacrylate and methylmethylacrylate. MW 20000, e.g. Plastoid B from Röhm, Darmstadt, Germany (hereinafter polymer B).
2) Polymers of acrylate and methacrylate esters containing methyl and ethyl neutral ester groups and trimethylaminoethyl cationic ester groups. Chloride ions may be present. Mean Molecular weight 150000 Daltons. Viscosity (20° C.), maximum 15 cP. Refractive index 1.380–1.385. Density 0.815–0.835 g/cm^3. Ratio of cationic ester groups to neutral alkyl groups 1:20 giving an alkali count of 28.1 mg KOH per gram polymer (Eudragit RL 100 Registered Trade Mark available from Röhm) or 1:40 giving an alkali count of 15.2 mg KOH per gram polymer (Eudragit RS 100 Registered Trade Mark, also available from Röhm).
3) Polymers of methacrylate esters containing trimethylaminoethyl cationic ester groups and other neutral (C_{1-4})alkyl ester groups. Chloride ions may be present. Mean molecular weight 150,000. Viscosity (20° C.) 10 cP. Refractive Index 1.38. Density 0.815. Alkali number of 180 mg KOH per gram polymer (Eudragit E 100, Registered Trade Mark, also available from Röhm and hereinafter referred to a polymer C).

If desired the pharmaceutical composition may contain other additives, such as plasticizers and/or softeners preferably skin compatible tensides, e.g. to provide flexibility to the pharmaceutical composition, and/or to dissolve partially or totally compound A.

Examples of additives include:

1) Polyoxyethylene fatty alcohol ethers. The alcohol may e.g. be a C_{12-18} alcohol. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(10) oleyl ether. A suitable ether may have a viscosity (25° C.) of about 100 cP, a solidification point of about 16° C., an HLB value of 12.4 and an acid count maximum 1.0 (Brij 97 Registered Trade Mark available from Atlas Chemie, Germany).
2) Polyoxyethylene Sorbitan fatty acid esters. The fatty acid may be e.g. a C_{12-18} fatty acid. The HLB value

may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(20) sorbitan monooleate, e.g. Tween 80, Registered Trade Mark available from Atlas Chemie, Germany.

3) Polyoxyethylene-(5-40) stearic acid esters, e.g. Myrj (Registered Trade Mark) available from Atlas Chemie, Germany.

4) Polyoxyethylene glycol fatty alcohol ethers, e.g. polyethylene glycol-(6-25) cetyl ether, glycerin polyethylene ricinoleate, glycerin polyethylene glycol stearate (Cremophor brand, Registered Trade Mark available from BASF Germany).

5) Polyoxyethylene glycols of MW from 200 to 600 Daltons, e.g. 300 or 400 Daltons.

6) Esters of poly(2-7)ethylene glycol glycerol ether having at least one hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid, e.g. Polyethylene glycol-(7) glyceryl cocoate, e.g. Cetiol HE, Registered Trade Mark, from Henkel, Germany.

7) Adipic acid lower alkyl esters, e.g. di-n-butyl adipate and diisopropyl adipate.

8) Glycerin polyethylene glycol ricinoleate, e.g. Product of 35 moles ethylene oxide and castor oil, e.g. Brand Cremophor EL Registered Trade Mark, obtainable from BASF, Germany.

9) Triacetin-(1,2,3).

10) Fatty acid, e.g. a C_{12-18} fatty acid.

11) Fatty alcohol, e.g. a C_{12-18} fatty alcohol.

The amount and type of additive required may depend on a number of factors, e.g. the HLB value of the tenside and the flexibility of the pharmaceutical required. The amount of additive does not significantly influence the capability of the polyacrylate to form films. Generally the weight ratio of tenside to the polymer may be from about 1:10 to 5:1, e.g. 1:10 to 1:3.

Preferably, however, no such additive is present or is only present in an amount less than 1% by weight based on the total weight of the pharmaceutical composition.

The pharmaceutical composition may contain skin penetration promoters, e.g. 1-dodecylazacycloheptan-2-one (azone) and N,N-diethyl-m-toluamide (DEET).

The amount and type of skin penetration promoter, and/or additives present may depend on a number of factors. Generally the weight ratio of skin penetration promoting agent to hydrophilic polymer will be from about 1:1 to 1:10. Preferably the amount of tenside and/or skin penetration promoter may be from about 3 to about 50%, preferably 20 to 40% by weight of the pharmaceutical composition.

Preferably however no such additive is present or is only present in an amount less than 1% by weight of the pharmaceutical composition.

If desired the pharmaceutical composition may contain a hydrophobic elastomer, e.g. a synthetic resin. Such resins are conventional in the plaster art. Suitable resins may include non-swellable acrylate resins. These may if desired be adhesive. The weight ratio of polymer, e.g. hydrophilic polymer to resin may for example be from 1:0.5 to 1:10. The resin may contain modifiers, extenders, e.g. of softening point about 50 to 100° C. Such extenders may have adhesive or softening properties. Examples of such extenders may include resin acids, glyceryl and phthalate esters of resin acids.

A preferred pharmaceutical composition according to the invention comprises

a) (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate as compound A in free base form in an amount of 20 to 40 weight-%,

b) polymethacrylate in an amount of 10 to 30% by weight

c) acrylate copolymer in an amount of 40 to 60% by weight, and

d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

In another aspect the present invention provides the use of an anti-oxidant to stabilize a pharmaceutical composition containing Compound A.

Before the finding by the present applicant that an anti-oxidant is necessary in compositions of this invention, it was hitherto thought unnecessary.

The applicant has found that an effective stabilising effect is surprisingly achieved when the anti-oxidant is selected from tocopherol, esters thereof, e.g. tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably α-tocopherol or ascorbyl palmitate. The antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5%, e.g. 0.05 to 0.20, e.g. 0.15%, more particularly 0.1% by weight based on the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention produced in analogous manner to example 1 described hereinafter containing 0.1% tocopherol show for Example only 1.3% degradation products compared to 4.46% degradation products in equivalent compositions not containing tocopherol in 2 month stress tests at 60° C. Pharmaceutical compositions of the invention in analogous manner to example 1 described hereinafter containing 0.15% tocopherol show for example only 0.25% degradation products compared to 1.09% degradation products in compositions not containing tocopherol in 3 month stress tests at 40° C. at 75% room humidity.

The pharmaceutical composition of the invention is preferably used for transdermal application.

In another aspect of the invention there is provided a transdermal device for administering a Compound A which comprises a pharmaceutical composition containing Compound A, a backing layer providing support for the pharmaceutical composition, an adhesive for fixing the pharmaceutical composition to the backing layer and a release-liner releasably contacting said adhesive.

The pharmaceutical composition may be conveniently contained in a discrete thin layer, the upper and lower surfaces of which may be coated in a layer of adhesive the surface of which in turn provide backing layer and release-liner contacting surfaces.

The pharmaceutical composition contained in the discrete layer may comprise the Compound A and other excipients in a polymer matrix, the polymer matrix therefor being provided by the diluent or carrier aforementioned. If desired Compound A may be dispersed throughout, or dissolved in, said polymer matrix.

The transdermal device may alternatively be of a more simple construction wherein the polymer matrix containing the pharmaceutical composition additionally comprises an adhesive. In such a simple construction there is no need for the layers of the aforementioned adhesive in order to fix and releasably fix respectively the backing layer and release-liner as the polymer matrix containing the Compound A is self adhesive.

The thickness of the pharmaceutical composition layer in a transdermal device may be in the order of from 20 to 100 μm, more preferably 60 to 100.

The backing layer is preferably made of poly(ethylene terephthalate) PET foil. The backing layer should be thick

enough to resist wrinkling which may arise upon prolonged periods in storage and through the movement of a subject's skin. Typically, the backing layer is, e.g. from approximately 10 μm to 15 μm, in thickness.

In a preferred embodiment, the backing layer is a double layer which consists of a PET layer as aforementioned and an EVA layer, e.g. Scotch Pack 1012.

The release-liner may be a disposable element which serves to protect the pharmaceutical composition prior to its application. Typically the release-liner is produced from a material impermeable to compound A, and adhesive. This release-liner may be easily stripped away from the adhesive. A preferred release-liner is made of poly(ethylene terephthalate) PET foil. A release-liner, e.g. of about 50 to 250 μm, e.g. 100 μm thickness PET film, may be applied over the pharmaceutical composition.

The release liner may be silicone-coated. Said coating is preferably formed of any fluorosilicone compound which is conventionally used in the art, e.g a polyfluoroalkylsiloxane.

It is particularly preferred to employ such a fluorosilicone coating when the adhesive used to affix the pharmaceutical composition to the release liner is not itself a silicone adhesive.

The adhesive may be chosen from any adhesive suitable for skin contact and is preferably an adhesive in which Compound A dissolves at least partly. Preferably the adhesive is a contact adhesive which is pressure sensitive. Preferred adhesive are chosen from amine-resistant silicone pressure sensitive adhesives known in the art, for example the BIO-PSA adhesives produced by Dow Coming Corporation, in particular BIO-PSA Q7-4302.

In a very simple construction of the transdermal device, the adhesive may in fact be the polymer of the polymer matrix.

In a further embodiment, the invention provides a transdermal device comprising a backing layer, a layer comprising compound A in a polymer matrix, a release-liner and, disposed between the layer comprising compound A in a polymer matrix and the release liner, a discrete layer of adhesive material for releasably fixing said transdermal device to patients skin.

Preferably, the adhesive material is a silicone adhesive chosen from amine-resistant silicone pressure sensitive adhesives as hereinabove described.

Typically, a transdermal device of said further embodiment comprises:

a) a polymethacrylate backing layer

b) Compound A in free base form in an acrylate copolymer

c) a BIO-PSA Q7-4302 silicone adhesive layer

d) a release-liner.

Preferably, said further embodiment also comprises silicone oil, e.g. silicone oil Q7-9120 from Dow Coming Corporation, in an amount of 0.1 to 5% by weight, e.g. 1%. The backing layer thickness is preferably from 10 to 50 μm, e.g. 23 μm, and has preferably a round shape.

In general transdermal devices of the invention may be produced in a simple manner. A solvent-evaporation process may be used for said compositions. Thus all the ingredients of the pharmaceutical composition may be mixed in a solvent, e.g. acetone, ethylacetate or hexane, and cast onto a substrate which may act as the backing layer or the release-liner.

The transdermal device aforementioned may be conveniently formed in continuous sheets and may be cut into patches of any desirable size or configuration before use. However, the patches so-formed may expose the pharmaceutical composition-containing layer of the laminate to the atmosphere at the outer edges of the patch.

In an alternative embodiment, however, a transdermal device is provided wherein in the patches formed therefrom, the pharmaceutical composition is not exposed to the atmosphere during storage or during application. Such patches further reduce the likelihood of the Compound A being exposed to oxidative influences. The transdermal device may comprise, e.g. a continuous backing layer, a continuous release-liner and located there-between, in discrete portions, a pharmaceutical composition portion, the backing layer being configured such that it may be releasably fixed with an adhesive to the release-liner so to seal said pharmaceutical composition in a pocket defined by the inner surface of the backing layer and inner surface of the release-liner. This embodiment may be conveniently referred to as a cover patch.

The pocket described hereinabove is preferably filled with an adhesive so as to encapsulate completely the discrete portion of pharmaceutical composition. Preferably the adhesive is a silicone pressure sensitive adhesive as described hereinabove.

It is an optional feature of all the transdermal devices described hereinabove that they comprise a layer of adhesive between the pharmaceutical composition and the release liner. This, has the primary function of fixing the release liner in contact with the remainder of the device thus protecting the pharmaceutical composition before use. However, if the adhesive is a silicone adhesive, then the layer may additionally act as a membrane through which the Compound A may pass at a controlled rate into the patient through the skin. Without wishing to be limited to a particular theory, it is suggested that the Compound A, dispersed throughout the polymer matrix exhibits little tendency to migrate into the silicone adhesive layer during storage. Accordingly, there is relatively low concentration of Compound A in the silicone layer. In use, the subjects skin, however, may display a much higher affinity for Compound A than the silicone layer and the initial low concentration of Compound A in the silicone layer passes into the subject's body. The silicone layer surprisingly prevents the subject from receiving a sudden high dose of Compound A upon application of the device and instead promotes a gradual increase of concentration in the subject.

The cover patch transdermal device may conveniently be formed as a continuous sheet or webbing and may be cut, or torn along a frangible area dividing each device, into patches before use although such devices may be provided as discrete patches.

The transdermal devices of the invention in general have, for example an effective contact area of pharmaceutical composition on the skin of from about 1 to about 80 square centimeters, preferably about 10 square centimetres, and are intended to be applied at intervals of about once every 1 to 7 days, preferably 1–3 days. Compound A is well tolerated at a dose of 36 mg in free base form in up to 80 cm^2 of patches according to the invention containing 36 mg compound A from which 12 mg was absorbed. Compound A may, for example be administered at a dose of 8 mg in a patch of ca. 10 cm^2, once every day. The patch may be applied, for example on the abdomen, thigh, behind an ear, or on a shoulder or upper arm.

The pharmaceutical composition, optionally formed as a transdermal device, of the present invention are useful for the same indications as for known compositions containing compound A. The exact amounts of compound A to be administered may depend on a number of factors, e.g. the

drug release characteristics of the compositions, the drug penetration rate observed in vitro and in vivo tests, the duration of action required, the form of compound A, and for transdermal compositions the size of the skin contact area, and the part of the body to which the unit is fixed. The amount of and, e.g. area of the composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound.

Orally, the Compound A is well tolerated at an initial dose of 1.5 mg twice a day orally and the dose may be stepped up to 3 mg twice daily in week 2. Higher dosages are possible, for example 4.5 mg twice daily and even 6 mg twice daily. Tolerability is seen to be even better for the transdermal device, wherein 24 mg were absorbed in 24 hours.

The following example illustrates the invention.

EXAMPLE 1

A composition is prepared consisting of the following components (by weight)

	(I)	(II)
Compound A	30%	30%
Polymer	20% (A)	20% (D)
Methacrylate	49.85% (B)	49.85% (C)
α-tocopherol	0.15%	0.15%

The components are added to ethyl acetate and mixed to give a viscous mass. The mass is spread onto a 100 μm transparent PET foil to produce a film 60 μm thick. A 15 μm thick PET foil release-liner is applied onto the dried mass. The patch is cut up into patches 10, 20, 30 or 40 cm^2 in area.

The liner is removed before application to the skin.

The compositions and devices of this invention provide storage stable systems. Insignificant degradation is detected after storage of up to 6 months at room temperature.

EXAMPLE 2

A composition is prepared according to Example 1 with Ascorbyl-palmitate instead of α-tocopherol. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 3

A composition is prepared according to Example 1 with a mixture of Ascorbyl-palmitate and α-tocopherol instead of α-tocopherol alone. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 4

A two-parts composition is prepared consisting of the following components

	Composition per unit (10 cm^2)	
Compound A	18 mg	30%
Polymer	29.94 mg	49.85%
Methacrylate	12 mg	20%
α-tocopherol	0.06	0.1%
Total 1st part (area weight 60 mg/10 cm^2)	70 mg	100%
and		
Bio-PSA Q7-4302	29.67 mg	98.9%
Silicone oil Q7-9120	0.3 mg	1.0%
α-tocopherol	0.03 mg	0.1%
Total 2nd part (area weight 30 mg/10 cm^2)	30 mg	100%

The two parts are then put together in the form of a patch.

What is claimed is:

1. A pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

2. The composition according to claim **1** wherein the antioxidant is selected from the group consisting of tocopherol, esters of tocopherol, ascorbic acid, esters of ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, propyl gallate, and combinations thereof.

3. The composition according to claim **2** wherein the antioxidant is α-tocopherol or ascorbyl palmitate.

4. The composition according to claim **1** wherein the antioxidant is present in an amount of from 0.05 to 0.2 weight percent.

5. The composition according to claim **4** wherein the antioxidant is present in an amount of from 0.1 to 0.15 weight percent.

6. A pharmaceutical composition comprising 7 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base; 10 to 30 weight percent of polymethacrylate or acid addition salt; 0.05 to 0.3 weight percent of α-tocopherol, wherein the weight percents are based on the total weight of the composition.

7. A transdermal device comprising a pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbarnate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

8. The transdermal device according to claim **7** further comprising an antioxidant; a backing layer providing support for the pharmaceutical composition; an adhesive for contacting and fixing the pharmaceutical composition to the backing layer; and a release liner releasably contacting said adhesive.

9. The transdermal device according to claim **7** comprising a backing layer; a layer comprising (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate and an antioxidant in a polymer matrix; a release liner; and an adhesive layer between the layer comprising (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in a polymer matrix and the release liner, wherein the adhesive layer releasably fixes the transdermal device to a patients skin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

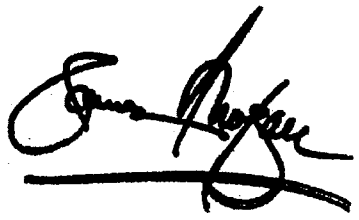
PATENT NO. : 6,316,023 B1
DATED : November 13, 2002
INVENTOR(S) : Asmussen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8,
Line 1, should read -- A pharmaceutical compostion comprising 20 to 40 --.
Line 3, should read -- Ethyl-3-[(1dimethylamino)ethyl]-N-methylphenyl carba- --.
Line 4, should read --mate in the form of a free base or acid addition salt, 0.01 to --.

Signed and Sealed this

Twenty-fifth Day of March, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT C

US006335031B1

(12) **United States Patent**
Asmussen et al.

(10) **Patent No.: US 6,335,031 B1**
(45) **Date of Patent: Jan. 1, 2002**

(54) **TTS CONTAINING AN ANTIOXIDANT**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/291,498**

(22) Filed: **Apr. 14, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/EP99/00078, filed on Jan. 8, 1999.

(30) **Foreign Application Priority Data**

Jan. 12, 1998 (DE) 9800526

(51) **Int. Cl.**[7] **A61F 13/00**

(52) **U.S. Cl.** **424/449**; 424/448; 602/57; 602/60; 604/290; 604/305; 604/307

(58) **Field of Search** 424/449, 448; 602/57, 60; 604/290, 305, 307

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,602,176 A * 2/1997 Enz 514/490

FOREIGN PATENT DOCUMENTS

FR	2 611 707	9/1988
WO	98/30243	7/1998
WO	98/31356	7/1998

* cited by examiner

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(57) **ABSTRACT**

Pharmaceutical composition comprising (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in free base or acid addition salt form and an anti-oxidant. Said pharmaceutical compositions may be delivered to a patient using a transdermal delivery device.

20 Claims, No Drawings

TTS CONTAINING AN ANTIOXIDANT

This a continuation-in-part of application PCT/EP99/00078, filed Jan. 8, 1999. The entire contents of the PCT/EP99/00078 disclosure are incorporated herein by reference.

This invention relates to a pharmaceutical composition for systemic administration of a phenyl carbamate, e.g. by transdermal administration. In particular this invention relates to a pharmaceutical composition of the phenyl carbamate—(S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate—(hereinafter referred to as compound A) in free base or acid addition salt form as disclosed in published UK patent application GB 2 203 040, the contents of which are incorporated herein by reference.

Compound A is useful in inhibiting acetylcholinesterase in the central nervous system, e.g. for the treatment of Alzheimer's disease.

A transdermal composition in the form of a patch is described in Example 2 of GB 2,203,040 according to which compound A is mixed with two polymers and a plasticiser to form a viscous mass. This mass is applied to a foil which is cut into patches.

It has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen. The transdermal composition described in GB 2203040 has been found to degrade, possibly by oxidative degradation, despite the formation of an occlusive polymer matrix around compound A and its storage in air-tight packaging.

The present applicant has found that stable pharmaceutical compositions comprising compound A can now be obtained, which show insignificant degradation of compound A over a prolonged time period, e.g. 2 years, as indicated by standard tests, e.g. stress tests.

In one aspect, the invention provides a pharmaceutical composition comprising Compound A in free base or acid addition salt form and an anti-oxidant.

The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests.

The pharmaceutical compositions of the invention may contain high amounts of compound A, e.g. from 1 to 40% by weight, e.g. 10–35%, more particularly 20–35%, e.g. 30%.

The compound A may be in any of a wide variety of pharmaceutical diluents and carriers known in the art. The diluent or carrier may contain trace amounts of free radicals without affecting the stability of the pharmaceutical composition of the invention.

The diluent or carrier is preferably one or more polymers, more preferably a hydrophilic polymer or polymers. In a preferred embodiment the diluent of carrier is selected from at least one polymer selected from acrylate polymers, and polymethacrylate polymers. The polymers preferably have a mean molecular weight of from about 50,000 to about 300,000 Daltons, e.g. 100,000 to 200,000 Daltons. The polymers preferably are capable of forming a film, thus to be compatible to the skin.

As a polymer one can mention in particular an acrylate co-polymer, e.g. co-polymers of butyl acrylate, ethyl hexyl acrylate and vinyl acetate. Preferably the polymer is cross-linked. A preferred acrylate polymer is one of the Durotak brand available from National Starch and Chemical Company, Zutphen, Holland, e.g. Durotak 87-2353 (hereinafter polymer A), 387-2051 or 387-2052 (hereinafter polymer D).

The diluent or carrier is preferably present in an amount of up to 90%, more preferably 70% by weight base on the total weight of the pharmaceutical composition.

The polymer, when a hydrophilic polymer, may conveniently take up water and is permeable to water, e.g. moisture from the skin, although the polymer may be insoluble in water. The polymer may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum comeum at a pH of from 4 to 7, preferably at skin pH, e.g. around 5.5. If desired such polymers may be soluble in organic solvents.

Examples of suitable polymers include polyacrylamide and its co-polymers, polyvinylpyrrolidone (PVP), vinyl acetate/vinyl alcohol co-polymers, polyvinyl alcohol (PVA) and derivatives, ethyl cellulose and other cellulose and starch derivatives.

Hydrophilic polyacrylates are preferred polymers. The polyacrylate may be substituted, e.g. a methacrylate. They may be commercially available acrylate/methacrylate co-polymers. Some or all of the acid groups may be esterified, e.g. with alkyl (C_{1-10}) groups, more particularly alkyl groups having 1 to 4 carbon atoms such as methyl or ethyl groups.

Examples of commercially available polymers of this type include:

1) Polymers of methacrylate containing alkyl (C_{1-4}) ester groups. Preferably the polymer matrix is a mixture of an acrylate polymer and a methacrylate polymer e.g. in a weight ratio of from 5:1 to 1:1, e.g. 4:1 to 2:1 e.g. 3:1, e.g. butylmethylacrylate and methylmethylacrylate. MW 20000, e.g. Plastoid B from Röhm, Darmstadt, Germany (hereinafter polymer B).
2) Polymers of acrylate and methacrylate esters containing methyl and ethyl neutral ester groups and trimethylaminoethyl cationic ester groups. Chloride ions may be present. Mean Molecular weight 150000 Daltons. Viscosity (20° C.), maximum 15 cP. Refractive index 1.380–1.385. Density 0.815–0.835 g/cm^3. Ratio of cationic ester groups to neutral alkyl groups 1:20 giving an alkali count of 28.1 mg KOH per gram polymer (Eudragit RL 100 Registered Trade Mark available from Röhm) or 1:40 giving an alkali count of 15.2 mg KOH per gram polymer (Eudragit RS 100 Registered Trade Mark, also available from Röhm).
3) Polymers of methacrylate esters containing trimethylaminoethyl cationic ester groups and other neutral (C_{1-4})alkyl ester groups. Chloride ions may be present. Mean molecular weight 150,000. Viscosity (20° C.) 10 cP. Refractive Index 1.38. Density 0.815. Alkali number of 180 mg KOH per gram polymer (Eudragit E 100, Registered Trade Mark, also available from Röhm and hereinafter referred to a polymer C).

If desired the pharmaceutical composition may contain other additives, such as plasticizers and/or softeners preferably skin compatible tensides, e.g. to provide flexibility to the pharmaceutical composition, and/or to dissolve partially or totally compound A.

Examples of additives include:

1) Polyoxyethylene fatty alcohol ethers. The alcohol may e.g. be a C_{12-18} alcohol. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(10) oleyl ether. A suitable ether may have a viscosity (25° C.) of about 100 cP, a solidification point of about 16° C., an HLB value of 12.4 and an acid count maximum 1.0 (Brij 97 Registered Trade Mark available from Atlas Chemie, Germany).
2) Polyoxyethylene Sorbitan fatty acid esters. The fatty acid may be e.g. a C_{12-18} fatty acid. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-

(20) sorbitan monooleate, e.g. Tween 80, Registered Trade Mark available from Atlas Chemie, Germany.

3) Polyoxyethylene-(5-40) stearic acid esters, e.g. Myrj (Registered Trade Mark) available from Atlas Chemie, Germany.

4) Polyoxyethylene glycol fatty alcohol ethers, e.g. polyethylene glycol-(6-25) cetyl ether, glycerin polyethylene ricinoleate, glycerin polyethylene glycol stearate (Cremophor brand, Registered Trade Mark available from BASF Germany).

5) Polyoxyethylene glycols of MW from 200 to 600 Daltons, e.g. 300 or 400 Daltons.

6) Esters of poly(2-7)ethylene glycol glycerol ether having at least one hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid, e.g. Polyethylene glycol-(7) glyceryl cocoate, e.g. Cetiol HE, Registered Trade Mark, from Henkel, Germany.

7) Adipic acid lower alkyl esters, e.g. di-n-butyl adipate and diisopropyl adipate.

8) Glycerin polyethylene glycol ricinoleate, e.g. Product of 35 moles ethylene oxide and castor oil, e.g. Brand Cremophor EL Registered Trade Mark, obtainable from BASF, Germany.

9) Tracetin-(1,2,3).

10) Fatty acid, e.g. a C_{12-18} fatty acid.

11) Fatty alcohol, e.g. a C_{12-18} fatty alcohol.

The amount and type of additive required may depend on a number of factors, e.g. the HLB value of the tenside and the flexibility of the pharmaceutical required. The amount of additive does not significantly influence the capability of the polyacrylate to form films. Generally the weight ratio of tenside to the polymer may be from about 1:10 to 5:1, e.g. 1:10 to 1:3.

Preferably, however, no such additive is present or is only present in an amount less than 1% by weight based on the total weight of the pharmaceutical composition.

The pharmaceutical composition may contain skin penetration promoters, e.g. 1-dodecylazacycloheptan-2-one (azone) and N,N-diethyl-m-toluamide (DEET).

The amount and type of skin penetration promoter, and/or additives present may depend on a number of factors. Generally the weight ratio of skin penetration promoting agent to hydrophilic polymer will be from about 1:1 to 1:10. Preferably the amount of tenside and/or skin penetration promoter may be from about 3 to about 50%, preferably 20 to 40% by weight of the pharmaceutical composition.

Preferably however no such additive is present or is only present in an amount less than 1% by weight of the pharmaceutical composition.

If desired the pharmaceutical composition may contain a hydrophobic elastomer, e.g. a synthetic resin. Such resins are conventional in the plaster art. Suitable resins may include non-swellable acrylate resins. These may if desired be adhesive. The weight ratio of polymer, e.g. hydrophilic polymer to resin may for example be from 1:0.5 to 1:10. The resin may contain modifiers, extenders, e.g. of softening point about 50 to 100° C. Such extenders may have adhesive or softening properties. Examples of such extenders may include resin acids, glyceryl and phthalate esters of resin acids.

A preferred pharmaceutical composition according to the invention comprises

a) (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate as compound A in free base form in an amount of 20 to 40 weight-%,

b) polymethacrylate in an amount of 10 to 30% by weight

c) acrylate copolymer in an amount of 40 to 60% by weight, and

d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

In another aspect the present invention provides the use of an anti-oxidant to stabilize a pharmaceutical composition containing Compound A.

Before the finding by the present applicant that an anti-oxidant is necessary in compositions of this invention, it was hitherto thought unnecessary.

The applicant has found that an effective stabilising effect is surprisingly achieved when the antioxidant is selected from tocopherol, esters thereof, e.g. tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably α-tocopherol or ascorbyl palmitate. The antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5%, e.g. 0.05 to 0.20, e.g. 0.15%, more particularly 0.1% by weight based on the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention produced in analogous manner to example 1 described hereinafter containing 0.1% tocopherol show for Example only 1.3% degradation products compared to 4.46% degradation products in equivalent compositions not containing tocopherol in 2 month stress tests at 60° C. Pharmaceutical compositions of the invention in analogous manner to example 1 described hereinafter containing 0.15% tocopherol show for example only 0.25% degradation products compared to 1.09% degradation products in compositions not containing tocopherol in 3 month stress tests at 40° C. at 75% room humidity.

The pharmaceutical composition of the invention is preferably used for transdermal application.

In another aspect of the invention there is provided a transdermal device for administering a Compound A which comprises a pharmaceutical composition containing Compound A, a backing layer providing support for the pharmaceutical composition, an adhesive for fixing the pharmaceutical composition to the backing layer and a release-liner releasably contacting said adhesive.

The pharmaceutical composition may be conveniently contained in a discrete thin layer, the upper and lower surfaces of which may be coated in a layer of adhesive the surface of which in turn provide backing layer and release-liner contacting surfaces.

The pharmaceutical composition contained in the discrete layer may comprise the Compound A and other excipients in a polymer matrix, the polymer matrix therefor being provided by the diluent or carrier aforementioned. If desired Compound A may be dispersed throughout, or dissolved in, said polymer matrix.

The transdermal device may alternatively be of a more simple construction wherein the polymer matrix containing the pharmaceutical composition additionally comprises an adhesive. In such a simple construction there is no need for the layers of the aforementioned adhesive in order to fix and releasably fix respectively the backing layer and release-liner as the polymer matrix containing the Compound A is self adhesive.

The thickness of the pharmaceutical composition layer in a transdermal device may be in the order of from 20 to 100 μm, more preferably 60 to 100.

The backing layer is preferably made of poly(ethylene terephthalate) PET foil. The backing layer should be thick enough to resist wrinkling which may arise upon prolonged periods in storage and through the movement of a subject's skin. Typically, the backing layer is, e.g. from approximately 10 μm to 15 μm, in thickness.

In a preferred embodiment, the backing layer is a double layer which consists of a PET layer as aforementioned and an EVA layer, e.g. Scotch Pack 1012.

The release-liner may be a disposable element which serves to protect the pharmaceutical composition prior to its application. Typically the release-liner is produced from a material impermeable to compound A, and adhesive. This release-liner may be easily stripped away from the adhesive. A preferred release-liner is made of poly(ethylene terephthalate) PET foil. A release-liner, e.g. of about 50 to 250 μm, e.g. 100 μm thickness PET film, may be applied over the pharmaceutical composition.

The release liner may be silicone-coated. Said coating is preferably formed of any fluorosilicone compound which is conventionally used in the art, e.g a polyfluoroalkylsiloxane.

It is particularly preferred to employ such a fluorosilicone coating when the adhesive used to affix the pharmaceutical composition to the release liner is not itself a silicone adhesive.

The adhesive may be chosen from any adhesive suitable for skin contact and is preferably an adhesive in which Compound A dissolves at least partly. Preferably the adhesive is a contact adhesive which is pressure sensitive. Preferred adhesive are chosen from amine-resistant silicone pressure sensitive adhesives known in the art, for example the BIO-PSA adhesives produced by Dow Corning Corporation, in particular BIO-PSA Q7-4302.

In a very simple construction of the transdermal device, the adhesive may in fact be the polymer of the polymer matrix.

In a further embodiment, the invention provides a transdermal device comprising a backing layer, a layer comprising compound A in a polymer matrix, a release-liner and, disposed between the layer comprising compound A in a polymer matrix and the release liner, a discrete layer of adhesive material for releasably fixing said transdermal device to patients skin.

Preferably, the adhesive material is a silicone adhesive chosen from amine-resistant silicone pressure sensitive adhesives as hereinabove described.

Typically, a transdermal device of said further embodiment comprises:

a) a polymethacrylate backing layer

b) Compound A in free base form in an acrylate copolymer

c) a BIO-PSA Q7-4302 silicone adhesive layer

d) a release-liner.

Preferably, said further embodiment also comprises silicone oil, e.g. silicone oil Q7-9120 from Dow Corning Corporation, in an amount of 0.1 to 5% by weight, e.g. 1%. The backing layer thickness is preferably from 10 to 50 μm, e.g. 23 μm, and has preferably a round shape.

In general transdermal devices of the invention may be produced in a simple manner. A solvent-evaporation process may be used for said compositions. Thus all the ingredients of the pharmaceutical composition may be mixed in a solvent, e.g. acetone, ethylacetate or hexane, and cast onto a substrate which may act as the backing layer or the release-liner.

The transdermal device aforementioned may be conveniently formed in continuous sheets and may be cut into patches of any desirable size or configuration before use. However, the patches so-formed may expose the pharmaceutical composition-containing layer of the laminate to the atmosphere at the outer edges of the patch.

In an alternative embodiment, however, a transdermal device is provided wherein in the patches formed therefrom, the pharmaceutical composition is not exposed to the atmosphere during storage or during application. Such patches further reduce the likelihood of the Compound A being exposed to oxidative influences. The transdermal device may comprise, e.g. a continuous backing layer, a continuous release-liner and located there-between, in discrete portions, a pharmaceutical composition portion, the backing layer being configured such that it may be releasably fixed with an adhesive to the release-liner so to seal said pharmaceutical composition in a pocket defined by the inner surface of the backing layer and inner surface of the release-liner. This embodiment may be conveniently referred to as a cover patch.

The pocket described hereinabove is preferably filled with an adhesive so as to encapsulate completely the discrete portion of pharmaceutical composition. Preferably the adhesive is a silicone pressure sensitive adhesive as described hereinabove.

It is an optional feature of all the transdermal devices described hereinabove that they comprise a layer of adhesive between the pharmaceutical composition and the release liner. This, has the primary function of fixing the release liner in contact with the remainder of the device thus protecting the pharmaceutical composition before use. However, if the adhesive is a silicone adhesive, then the layer may additionally act as a membrane through which the Compound A may pass at a controlled rate into the patient through the skin. Without wishing to be limited to a particular theory, it is suggested that the Compound A, dispersed throughout the polymer matrix exhibits little tendency to migrate into the silicone adhesive layer during storage. Accordingly, there is relatively low concentration of Compound A in the silicone layer. In use, the subjects skin, however, may display a much higher affinity for Compound A than the silicone layer and the initial low concentration of Compound A in the silicone layer passes into the subject's body. The silicone layer surprisingly prevents the subject from receiving a sudden high dose of Compound A upon application of the device and instead promotes a gradual increase of concentration in the subject.

The cover patch transdermal device may conveniently be formed as a continuous sheet or webbing and may be cut, or tom along a frangible area dividing each device, into patches before use although such devices may be provided as discrete patches.

The transdermal devices of the invention in general have, for example an effective contact area of pharmaceutical composition on the skin of from about 1 to about 80 square centimeters, preferably about 10 square centimeters, and are intended to be applied at intervals of about once every 1 to 7 days, preferably 1–3 days. Compound A is well tolerated at a dose of 36 mg in free base form in up to 80 cm^2 of patches according to the invention containing 36 mg compound A from which 12 mg was absorbed. Compound A may, for example be administered at a dose of 8 mg in a patch of ca. 10 cm^2, once every day. The patch may be applied, for example on the abdomen, thigh, behind an ear, or on a shoulder or upper arm.

The pharmaceutical composition, optionally formed as a transdermal device, of the present invention are useful for the same indications as for known compositions containing compound A. The exact amounts of compound A to be administered may depend on a number of factors, e.g. the drug release characteristics of the compositions, the drug penetration rate observed in vitro and in vivo tests, the duration of action required, the form of compound A, and for transdermal compositions the size of the skin contact area,

and the part of the body to which the unit is fixed. The amount of and, e.g. area of the composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound.

Orally, the Compound A is well tolerated at an initial dose of 1.5 mg twice a day orally and the dose may be stepped up to 3 mg twice daily in week 2. Higher dosages are possible, for example 4.5 mg twice daily and even 6 mg twice daily. Tolerability is seen to be even better for the transdermal device, wherein 24 mg were absorbed in 24 hours.

The following example illustrates the invention.

EXAMPLE 1

A composition is prepared consisting of the following components (by weight)

	(I)	(II)
Compound A	30%	30%
Polymer	20% (A)	20% (D)
Methacrylate	49.85% (B)	49.85% (C)
α-tocopherol	0.15%	0.15%

The components are added to ethyl acetate and mixed to give a viscous mass. The mass is spread onto a 100 μm transparent PET foil to produce a film 60 μm thick. A 15 μm thick PET foil release-liner is applied onto the dried mass. The patch is cut up into patches 10, 20, 30 or 40 cm^2 in area.

The liner is removed before application to the skin.

The compositions and devices of this invention provide storage stable systems. Insignificant degradation is detected after storage of up to 6 months at room temperature.

EXAMPLE 2

A composition is prepared according to Example 1 with Ascorbyl-palmitate instead of α-tocopherol. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 3

A composition is prepared according to Example 1 with a mixture of Ascorbyl-palmitate and α-tocopherol instead of α-tocopherol alone. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 4

A two-parts composition is prepared consisting of the following components

	Composition per unit (10 cm^2)	
Compound A	18 mg	30%
Polymer	29.94 mg	49.85%
Methacrylate	12 mg	20%
α-tocopherol	0.06	0.1%
Total 1st part (area weight 60 mg/10 cm^2)	70 mg	100%

-continued

	Composition per unit (10 cm^2)	
and		
Bio-PSA Q7-4302	29.67 mg	98.9%
Silicone oil Q7-9120	0.3 mg	1.0%
α-tocopherol	0.03 mg	0.1%
Total 2nd part (area weight 30 mg/10 cm^2)	30 mg	100%

The two parts are then put together in the form of a patch.

What is claimed is:

1. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A);

(b) about 0.01 to about 0.5 percent by weight of an antioxidant, based on the weight of the composition, and

(c) a diluent or carrier.

2. A pharmaceutical composition according to claim **1** containing 1 to 40% by weight of Compound A in free base or acid addition salt form.

3. A pharmaceutical composition according to claim **1** wherein the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.

4. A pharmaceutical composition according to claim **1** wherein the anti-oxidant is α-tocopherol or ascorbyl palmitate.

5. A pharmaceutical composition according to claim **1** wherein the anti-oxidant is tocopherol and is present in an amount of 0.1% by weight based on the weight of the pharmaceutical composition.

6. A pharmaceutical composition according to claim **1** comprising

(a) Compound A in free base form in an amount of 20 to 40% by weight,

(b) polymethacrylate in an amount of 10 to 30% by weight,

(c) acrylate copolymer in an amount of 40 to 60% by weight, and

(d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

7. A transdermal device comprising a pharmaceutical composition as defined in claim **1**, wherein the pharmaceutical composition is supported by a substrate.

8. A transdermal device according to claim **7**, wherein the pharmaceutical composition is located between an adhesive layer and the substrate.

9. A transdermal device according to claim **8**, wherein a release liner releasably contacts the adhesive layer.

10. The pharmaceutical composition of claim **1**, further comprising silicone oil.

11. A transdermal device comprising a backing layer, a layer comprising a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate (Compound A) and an amount of antioxidant effective to stabilize Compound A from degradation in a polymer matrix, a release-liner and, disposed between the layer comprising Compound A in a polymer matrix and the release-liner, a discrete layer of adhesive material for releasably fixing said transdermal device to a patient's skin.

12. The transdermal device of claim 1, wherein the discrete layer of adhesive material also comprises silicone oil.

13. The transdermal device of claim 1, wherein the antioxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, or propyl gallate.

14. The transdermal device of claim 1, wherein the antioxidant is α-tocopherol or ascorbyl palmitate.

15. A method of stabilizing (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A), wherein the method comprises forming a composition by combining Compound A with an amount of anti-oxidant effective to stabilize Compound A from degradation.

16. A method according to claim 15, wherein the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.

17. The method of claim 15, wherein the anti-oxidant is α-tocopherol or ascorbyl palmitate.

18. The method of claim 15, wherein the anti-oxidant is present in an amount of from about 0.01 to about 0.5% by weight based on the weight of the composition.

19. The method of claim 15, wherein α-tocopherol is present as the antioxidant in an amount of 0.1% by weight of the composition.

20. The method of claim 15, wherein the composition also comprises silicone oil.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,335,031 B1
DATED : January 1, 2002
INVENTOR(S) : Asmussen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [30], should read:
-- Jan. 12, 1998 (GB) ..... 9800526 --.

Item [56], **References Cited**, U.S. PATENT REFERENCES, should read:

-- 4,948,807	8/1990	Rosin et al.	514/484
5,344,656	9/1994	Enscore et al.	424/448
5,462,745	10/1995	Enscore et al.	424/448 --

Item [56], **References Cited**, FOREIGN PATENT REFERENCES, should read:

-- EP	427 741 B1	5/1991
WO	89/12470	12/1989 --

Column 9,
Lines 1-3, should read:

-- The transdermal device of claim 11, wherein the discrete layer of adhesive material also comprises silicone oil. --.
Lines 4-7, should read:

-- The transdermal device of claim 11, wherein the antioxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, or propyl gallate. --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,335,031 B1
DATED : January 1, 2002
INVENTOR(S) : Asmussen et al.

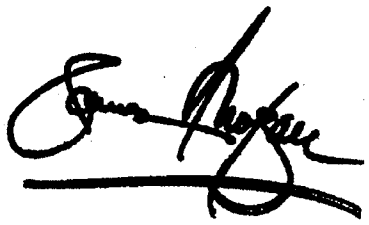
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 9, cont'd.
Lines 8-9, should read:

-- The transdermal device of claim 11, wherein the antioxidant is α-tocopherol or ascorbyl palmitate. --.

Signed and Sealed this

First Day of October, 2002



Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office